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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SULLIVAN, DANIEL M	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 12/30/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/057,726	OWENS ET AL.	
	Examiner	Art Unit	
	Daniel M Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 July 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35-58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 August 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This is the First Office Action on the Merits of the application filed 24 January 2002, which claims benefit of U.S. Provisional application 60/263,811, filed 24 January 2001, and is a continuation-in-part of U.S. Patent application 09/600,319, filed 13 July 2000, which is the U.S. National stage of International application PCT/US99/01038, filed 15 January 1999, which claims benefit of U.S. Provisional application 60/071,300 filed 16 January 1998. The amendments filed 24 June 2002 and 9 September 2003 have been entered. Claims 1-34 were canceled and claims 35-58 were added in the 9 September 2003 amendment. Claims 35-58 are pending and under consideration.

Election/Restrictions

Applicant's election with traverse of Group I in Paper No. 12, filed 7 July 2003 is acknowledged. The traversal is on the ground(s) that examination of the claims in Groups I-IV would not create an undue burden. Applicant states, "the Examiner must show that examination of the claims would involve substantially different prior art searches, making the co-examination burdensome" (page 5). This is not found persuasive because, as pointed out in the previous Office Action, the groups are directed to subject matter having separate status in the art, which clearly shows that examination of the claims would involve substantially different prior art searches. Thus examination of additional groups in a single application would impose an undue burden on the Office.

The requirement is still deemed proper and is therefore made FINAL.

Drawings

The drawings are objected to because the formal drawings filed 23 August 2002 do not contain Figure 25. It is therefore unclear whether Applicant intends that Figure 25 be deleted from the disclosure. If that is the case, the specification should be amended to omit the brief description of Figure 25. Clarification is requested. The objection to the drawings will not be held in abeyance.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

Specifically, there is no descriptive support for the instant claims in the application 09/600,319. Although the application discloses smooth muscle cell myosin heavy chain promoter/enhancer sequences, it does not contemplate the heterologous TATA box or transcription initiation site, CArG motif mutations or promoter sequence deletions to which the instant claims are limited. Therefore, the claims are afforded benefit of U.S. Provisional application 60/263,811, filed 24 January 2001, only.

Claim Objections

Claim 35 objected to because of the following informalities: The claim is limited to a particular nucleic acid sequence by reference to a drawing. Incorporation of a claim limitation by reference to a specific figure is permitted only in exceptional circumstances where there is no practical way to define the invention in words and where it is more concise to incorporate by reference than duplicating a drawing or table into the claim. See MPEP 2173.05(s). In the instant case, the subject matter is more concisely incorporated into the claim by reference to the sequence listing. The claim should be amended to precisely indicate where the sequence limitation can be found in the sequence listing. In the interest of compact prosecution, the claims have been searched based on the description of the sequences found in the legend of Figure 18(b) and at page 23, lines 16-26.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 45 and 57 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims are directed to a genetically engineered cell. The meets and bounds of the genetically engineered cell of the claims are not defined in such a way as to exclude the genetically engineered animal contemplated in the specification at page 30, lines 12-13 and page 33, lines 20-25. Further, the transgenic animal is not defined in such a way as to exclude a transgenic human. Therefore, the broadest reasonable interpretation of the claim

encompasses a transgenic human, which is non-statutory subject matter. Amending the claims such that they are directed to an "isolated' genetically engineered cell would overcome this rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 35-58 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

In the instant case, the claims are directed to isolated polynucleotides comprising portions of the smooth muscle cell myosin heavy chain (SM-MHC) promoter/enhancer from rat or human, wherein the promoter/enhancer initiates expression in a smooth muscle cell *in vivo* when

introduced into an animal. Some nucleic acids of the claims are particularly limited to comprising a portion of the rat SM-MHC promoter/enhancer corresponding to +1422 to +1696, relative to the transcriptional start site, or a portion of the human SM-MHC promoter/enhancer corresponding to +1776 to +2072, relative to the transcriptional start site. Other nucleic acids are limited to comprising the nucleic acid sequences set forth as SEQ ID NO: 16 or 17 wherein a CArG2 or intronic CArG motif is mutated, and wherein the promoter is expressed in a "subset" of smooth muscle cells *in vivo* when introduced into an animal. Still other nucleic acids are limited to comprising nucleotides 1 to 6700 and 11,700 to 13,700 or 1 to 6700 and 11,700 to 15,800 of the rat SM-MHC promoter enhancer (SEQ ID NO: 16), wherein the prompter is expressed in a "subset" of smooth muscle cells *in vivo* when introduced into an animal.

Given their broadest reasonable interpretation, the claims are generic to: any nucleic acid comprising the nucleic acid sequence found at +1776 to +2072 of the human SM-MHC or +1422 to +1696 of the rat SM-MHC, and capable of providing expression in a smooth muscle cell *in vivo* when introduced into any animal; a nucleic acid comprising SEQ ID NO: 16 or 17 wherein any mutation of any CArG2 or intronic CArG motif provides expression in any subset of smooth muscle cells in any animal; or a nucleic acid comprising 1 to 6700 and 11,700 to 13,700 or 1 to 6700 and 11,700 to 15,800 of the rat SM/MHC promoter enhancer, wherein the promoter is expressed in any subset of smooth muscle cells *in vivo* when introduced into any animal.

The Guidelines for Written Description state: "when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus" (Federal Register, Vol. 66, No. 4, Column 3, page 1106). "The written description requirement for a claimed genus may be satisfied through sufficient description of a

representative number of species by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus" (MPEP §2163(3)(a)(ii)).

First, it should be pointed out that, although the art teaches nucleic acids comprising the various sequences set forth in the application (see, e.g., Madsen *et al.* (1998) *Circ. Res.* 82:908-917, made of record in the IDS filed 16 August 2002, or GenBank Accession No. U91323), the art does not teach that the sequence limitations set forth in the claims provide smooth muscle cell expression *in vivo* or expression in a subset of smooth muscle cells *in vivo* as recited in the claims. Thus, nucleic acids having the properties set forth in the claims are not conventional in the art.

With regard to nucleic acid comprising the nucleic acid sequence found at +1776 to +2072 of the human SM-MHC, and capable of providing expression in a smooth muscle cell *in vivo*, the specification teaches that the –5.1 to +13.5 region of a human SM-MHC promoter/enhancer provides smooth muscle specific expression in a transgenic mouse (see especially Figure 9 and the description thereof on page 8), and that a portion of the rat SM-MHC promoter/enhancer corresponding to +1422 to +1696, relative to the transcriptional start site, is sufficient to confer smooth muscle specific expression in a transgenic mouse (see especially page 56, lines 10-13 and the paragraph bridging pages 58-59). However, these teachings fail to adequately describe the genus of nucleic acids comprising the nucleic acid sequence found at +1776 to +2072 of the human SM/MHC or the nucleic acid sequence found at +1422 to +1696 of

the rat SM/MHC, and capable of providing expression in a smooth muscle cell *in vivo* when introduced into any animal.

As discussed in detail herein below, the art teaches that the structural requirements for smooth muscle specific expression *in vivo* are complex and poorly defined. Although the instant disclosure establishes that the portion of the rat SM-MHC promoter from +1422 to +1696 of the rat SM-MHC promoter/enhancer is sufficient to provide smooth muscle expression in a transgenic mouse, this teaching alone fails to establish a nexus between the structural and functional properties of the claimed nucleic acids that adequately describes the full scope of the claim. First, the sequence alignment set forth as Figure 18B reveals significant differences in the rat and human sequences and, because promoters are comprised of regulatory elements having stringent sequence requirements, the skilled artisan would not be able to predict that the sequence fragment disclosed for the human would function the same as that of the rat. Likewise, the skilled artisan would not be able to envision the full scope of nucleic acids comprising the disclosed sequences and capable of providing smooth muscle cell expression in any animal because there is no evidence that the sequences to which the claims are limited are sufficient to provide smooth muscle cell expression in all animals, and the skilled artisan would not know what additional sequences must also be comprised in the nucleic acid to provide smooth muscle expression in animals other than mice. Therefore, the disclosure provides adequate description only for claims limited to comprising the portion of the rat SM-MHC promoter from +1422 to +1696 of the rat SM-MHC promoter/enhancer is sufficient to provide smooth muscle expression in a transgenic mouse.

With regard to nucleic acids comprising mutations in a CArG2 or intronic CArG motif wherein the promoter is expressed in a "subset" of smooth muscle cells *in vivo* when introduced into an animal, the specification teaches a nucleic acid comprising SEQ ID NO: 16 wherein an intronic CArG sequence at residues 5815-5824 is changed from CCTTGTATGG to AGGCCTATGG or the CArG2 sequence at residues 3105-3114 is changed from TTCCTTTTATGG to GGATCCTATGG (page 32, lines 15-24). In Table 1, the specification sets forth the expression pattern of these promoters in a transgenic mouse. Again, however, given the complexity of the structural requirements for smooth muscle cell expression the skilled artisan could not readily envision the full scope of the nucleic acids encompassed by the claims. First, the CArG motifs of the claims are not limited to any particular CArG2 or intronic CArG (i.e., the sequences found at 5815-5824 or 3105-3114 of SEQ ID NO: 16). Therefore, the claims encompass mutations at CArG sequences anywhere within or beyond the boundaries of the sequences disclosed as SEQ ID NO: 16 or 17. The skilled artisan could not possibly envision the effects of mutating CArG sequences outside of those found in SEQ ID NO: 16 at 5815-5824 or 3105-3114. In addition, as above, there is no evidence that the mutations reduced to practice with the rat promoter would have the same effect in the human promoter and the specification does not disclose the requirements for expression in a subset of smooth muscle cells *in vivo* in any animal other than a mouse. Finally, the specification only describes a promoter capable of providing expression in the subsets of mouse smooth muscle cells set forth in Table 1. For example, there is no description of a nucleic acid comprising the structural limitations of the claims, which is expressed only in aorta. Therefore, the skilled artisan would not know what additional structural features must also be comprised by the nucleic acids to provide expression

in subsets other than those set forth in Table 1. For these reasons, the disclosure provides descriptive support only for a nucleic acid comprising a SM-MHC promoter enhancer comprising SEQ ID NO: 16, wherein the intronic CArG sequence at residues 5815-5824 is changed from CCTTGTATGG to AGGCCTATGG or the CArG2 sequence at residues 3105-3114 is changed from TTCCTTTTATGG to GGATCCTATGG and wherein the promoter comprising said intronic CArG sequence mutation is expressed in coronary artery, mesenteric artery, vena cava, airways, stomach, intestine and bladder but not aorta, and wherein the promoter comprising said CArG2 mutation is expressed in mesenteric artery, airway, stomach, intestine and bladder but not in aorta, coronary artery, or vena cava.

With regard to a nucleic acid comprising 1 to 6700 and 11,700 to 13,700 or 1 to 6700 and 11,700 to 15,800 of the rat SM/MHC promoter enhancer, wherein the promoter is expressed in any subset of smooth muscle cells *in vivo* when introduced into any animal, the specification teaches that nucleic acids comprising these sequences are expressed in bladder and gastrointestinal smooth muscle cells but not in vascular smooth muscle cells. However, for reasons discussed above, these teachings do not provide adequate descriptive support for nucleic acids comprising the structural limitations set forth and capable of conferring smooth muscle expression in subsets other than the subset specifically described in the specification or in animals other than mice. Given the complex and poorly defined nature of the structural requirements for smooth muscle specific expression *in vivo*, the skilled artisan would not be able to readily envision those nucleic acids encompassed by the claims that are capable of providing smooth muscle expression in a subset of smooth muscle cells in any animal other than a mouse or capable of providing expression in a subset other than what is disclosed in the specification.

Therefore, the specification provides descriptive support only for nucleic acids comprising 1 to 6700 and 11,700 to 13,700 or 1 to 6700 and 11,700 to 15,800 of the rat SM-MHC promoter/enhancer, wherein the promoter is expressed in bladder and gastrointestinal smooth muscle cells but not in vascular smooth muscle cells *in vivo* when introduced into a mouse.

Although the specification provides guidance as to how the nucleic acids encompassed by the claims might be identified (especially the section entitled "Isolation of SM specific promoter sequences" beginning on page 25), an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself. It is not sufficient to define DNA solely by its principal biological property (i.e. it provides smooth muscle specific expression *in vivo*) because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any DNA with that biological property. Also, naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, claiming all DNA's that achieve a result without defining what means will do is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)).

In view of these considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate to its scope because it does not provide adequate written description for the broad class of nucleic acids comprising the structural limitations set forth and providing expression in a smooth muscle cell, or subset of smooth muscle cells, *in vivo* when introduced

into an animal. Therefore, only the described nucleic acids (*Id.*) meet the written description provision of 35 U.S.C. §112, first paragraph.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 35-58 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

a nucleic acid comprising the portion of the rat SM-MHC promoter from +1422 to +1696 of the rat SM-MHC promoter/enhancer, wherein the promoter/enhancer initiates expression in a smooth muscle cell *in vivo* when introduced into a mouse;

a nucleic acid comprising a SM-MHC promoter enhancer comprising SEQ ID NO: 16, wherein the intronic CArG sequence at residues 5815-5824 is changed from CCTTGTATGG to AGGCCTATGG or the CArG2 sequence at residues 3105-3114 is changed from TTCCTTTTATGG to GGATCCTATGG and wherein the promoter comprising said intronic CArG sequence mutation is expressed in coronary artery, mesenteric artery, vena cava, airways, stomach, intestine and bladder but not aorta, and wherein the promoter comprising said CArG2 mutation is expressed in mesenteric artery, airway, stomach, intestine and bladder but not in aorta, coronary artery, or vena cava *in vivo* when introduced into a mouse; and

a nucleic acids comprising 1 to 6700 and 11,700 to 13,700 or 1 to 6700 and 11,700 to 15,800 of the rat SM-MHC promoter/enhancer, wherein the promoter is expressed in bladder and gastrointestinal smooth muscle cells but not in vascular smooth muscle cells *in vivo* when introduced into a mouse,

does not reasonably provide enablement for any nucleic acid comprising the rat or human sequence depicted in Figure 18(b), any nucleic acid comprising SEQ ID NO: 16 or SEQ ID NO: 17 and a mutation in a CArG2 or intronic CArG motif, or any nucleic acid comprising 1 to 6700 and 11,700 to 13,700 or 1 to 6700 and 11,700 to 15,800 of the rat SM-MHC promoter/enhancer, wherein the promoter/enhancer initiates expression in a smooth muscle cell or subset of smooth muscle cells *in vivo* when introduced into any animal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the invention and Breadth of the claims: The scope of the claimed subject matter is described herein above. To summarize, the claims are directed to nucleic acids comprising various fragments or modifications of the rat or human SM-MHC promoter/enhancer sequence, wherein the promoter is expressed in a smooth muscle cell or any subset of smooth muscle cells *in vivo* when introduced into any animal. The claims thus embrace nucleic acids having a broad range of functional activities, including smooth muscle expression *in vivo* in

unlimited species of animal and expression in an unlimited variety of subsets of smooth muscle cells.

State of the prior art and level of predictability in the art: The art teaches that, at the time the instant application was filed, the processes controlling smooth muscle specific expression and smooth muscle differentiation were poorly understood. Manabe *et al.* (2001) *J. Clin. Invest.* 107:823-834 (made of record in the IDS filed 16 August 2002) teaches, "[c]ell specification and differentiation can be considered as sequential and coordinate expression of an array of cell-specific/selective genes required for specialized cellular function. However, little is know regarding the mechanisms that control transcription during SMC differentiation" (paragraph bridging the left and right columns on page 823). Thus, Manabe *et al.* teaches that little was known regarding the mechanisms underlying regulated expression of smooth muscle cell specific genes as of 2001. Manabe *et al.* goes on to teach that, although variety of transcription factors have been identified as potential regulators of SMC-specific expression, the circuitry of transcription factors that control SMC-specific transcription remains a major unresolved issue. Manabe *et al.* teaches that the findings described therein demonstrate the multiplicity of regulatory programs that control expression of SMC-differentiation *in vivo*, suggest that each of the multiple CArG elements mediate distinct information for transcriptional regulation in different cell types *in vivo* and imply that the spatial and temporal regulation of SMC genes is not governed by a single regulatory region or an enhancer (paragraph bridging the left and right columns on page 832). Finally, Manabe *et al.* teach that their preliminary data indicate that the 5'-flanking and first intron of the SM-MHC promoter/enhancer contain multiple positive and negative transcriptional regulatory regions and that different SMC subtypes require different

subsets of modules. Viewed as a whole, the teachings of Manabe *et al.* clearly show that regulation of SMC-specific expression in general, and regulation of the SM-MHC promoter/enhancer in particular, involves the coordinated action of multiple regulatory factors and that these processes were poorly understood in 2001. In view of these teachings, the skilled artisan would not expect that the *in vivo* expression pattern observed using a nucleic acid comprising particular fragment or mutation of the SM-MHC promoter/enhancer could be used to predict the expression pattern of nucleic acids comprising other fragments or mutations because expression is determined by a multiplicity of regulatory programs and the spatial and temporal regulation of SMC genes is not governed by a single regulatory region, but instead require different subsets of modules.

Arnone *et al.* (1997) *Development* 124:1851-1864 teaches that the complex modular organization of *cis*-regulatory elements is a general feature of promoter/enhancer structure and that "[i]n terms of direct experimental evidence, the forms of these networks are just beginning to be perceptible" (sentence bridging the left and right columns on page 1851). Arnone *et al.* exemplifies this complexity in Figure 1 and the caption thereto and teaches, "each of the modular elements portrayed in Fig. 1 consists of target sites for diverse factors, which execute diverse functions" (final paragraph on page 1853). Teachings found throughout Arnone *et al.* speak to the overall complex and integrated nature of *cis*-element organization. Thus, the skilled artisan could not readily predict the expression pattern obtained with any given fragment or mutation of the SM-MHC promoter.

Although the art does not speak directly to the predictability of obtaining smooth muscle expression in any animal using the claimed nucleic acids, given the broad scope of "an animal" it

is reasonable to expect that the disclosed nucleic acids lack regulatory elements that would be required for the recited function in many types of animal. Further, although the art also does not speak directly to the predictability of extending functional properties demonstrated using a rat SM-MHC promoter/enhancer to homologous regions in a human SM-MHC promoter/enhancer, the sequence alignment provided in Figure 18B shows significant structural differences between the rat and human sequence. Furthermore, the art teaches that the first intron of the human SM-MHC promoter/enhancer comprises at least one additional CArG element not described in the rat sequence (see Forsythe (1999) *FASEB J.* 13:A169), which raises the possibility that the number or positioning of regulatory elements in the promoter/enhancer are not identical in the rat and human.

Amount of direction provided by the inventor and existence of working examples: The specification teaches that the –5.1 to +13.5 region of a human SM-MHC promoter/enhancer provides smooth muscle specific expression in a transgenic mouse, and that a portion of the rat SM-MHC promoter/enhancer corresponding to +1422 to +1696, relative to the transcriptional start site, is sufficient to confer smooth muscle specific expression in a transgenic mouse (*Id.*). The specification further teaches a nucleic acid comprising SEQ ID NO: 16 wherein an intronic CArG sequence at residues 5815-5824 is changed from CCTTGTATGG to AGGCCTATGG or the CArG2 sequence at residues 3105-3114 is changed from TTCCTTTTATGG to GGATCCTATGG and the expression pattern of these promoters in a transgenic mouse (*Id.*). Finally, the specification teaches that a nucleic acid comprising 1 to 6700 and 11,700 to 13,700 or 1 to 6700 and 11,700 to 15,800 of the rat SM/MHC promoter enhancer is expressed in bladder and gastrointestinal smooth muscle cells but not in vascular smooth muscle cells (*Id.*).

However, the specification does not teach the skilled artisan how these findings can be readily extended to obtain a polynucleotide capable of providing expression in a smooth muscle cell in any animal, or capable of providing expression in subsets of smooth muscle cells other than those actually reduced to practice. Furthermore, the specification does not provide teachings that would enable the skilled artisan to readily predict the effects CArG element mutations other than the mutations reduced to practice in the rat sequence.

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: Although the relative level of skill in the art is high, the ordinary skilled artisan would not be able to make or use the full scope of the claimed invention without engaging in undue trial and error experimentation. The art teaches that the structural requirements of promoter function are highly complex and poorly understood. Therefore, extending the working examples of the instant disclosure to provide the full scope of the claimed subject matter could not be accomplished without empirical experimentation. First, with regard to making polynucleotides capable of expression in a smooth muscle cell *in vivo* in any animal, the skilled artisan would have to test the disclosed nucleic acids in a wide variety animals and would very likely have to identify additional, species specific regulatory elements required for smooth muscle expression in many species of animal. Likewise, making nucleic acids capable of expression in any subset of smooth muscle cells would require that the skilled artisan identify those regulatory elements that provide expression in each of the many possible subsets of smooth muscle cells.

With regard to nucleic acids comprising mutations or fragments of the SM-MHC promoter beyond those described in the working examples, the skilled artisan would not know

how to use these nucleic acids without first empirically making and testing each one because their functional characteristics cannot be predicted. That is, the specification provides several uses for the claimed nucleic acids but each of these requires that the functional characteristics of the nucleic acids are known. As the function is unpredictable and requires empirical experimentation to determine, using the claimed invention would require that the skilled artisan experiment unduly.

Thus, due to the art recognized unpredictability of the structural requirements of promoter/enhancer function and the lack of guidance in the specification or prior art with regard to how to make and use the full scope of the claimed subject matter, it would require undue experimentation to practice the invention commensurate with the full scope of the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 43, 44 and 47-58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 43 is indefinite because there is no definite or indefinite article preceding "promoter" in line 1. It is not clear whether the promoter referred to is the promoter of claim 40 or if it is generic to any promoter.

Claim 44 is indefinite in the recitation of "the heterologous polynucleotide" in line 1. There is no antecedent basis for the limitation in claim 40, from which it depends. Amending claim 44 to depend from claim 43 would be remedial.

Claims 47-49 are indefinite in reciting that the polynucleotide "does not comprise the intervening nucleotides". The limitation does not require that the nucleic acid not comprise the full sequence of nucleotides from 6701 to 11699 or 6701-9499. Therefore, it is unclear how much of the intervening sequence must be deleted to meet the claim. For example, would any single base deletion within the intervening sequence meet the limitation? It is suggested that the scope of the deletion be set forth in a positive statement such as: wherein the polynucleotide does not comprise 6701 to 11699 of SEQ ID NO: 16.

Allowable Subject Matter

Claims 35-58 are free of the art. Although the art teaches SM-MHC promoter/enhancer elements from rat (e.g., Madsen *et al.*(*supra*)) and human (e.g., GenBank Accession No. U91323), and CArG elements within the first intron of the human promoter/enhancer (e.g., Forsythe *et al.* (*supra*)), the art does not teach the particular structural and functional limitations of the claimed nucleic acid. Given the unpredictable nature of the relevant art, the limitations of the claims would not have been obvious to one of ordinary skill in the art at the time of filing.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 703-305-4448. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 703-305-1998. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Please note: Art Unit 1636 will be moving to the new USPTO facilities on 14 January 2004. After that date, Examiner Sullivan can be reached at 571-272-0779 and Examiner Yucel can be reached at 571-272-0781.

DMS

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PRIMARY EXAMINER